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THE EARLIEST ION CHANNELS IN PROTOCELLULAR MEMBRANES

Milan Mijajlovic, milan.mijajlovic@nasa.gov
NASA Ames Research Center, Moffett Field, California, United States
Andrew Pohorille, andrew.pohorille@nasa.gov
NASA Ames Research Center, Moffett Field, California, United States
Michael Wilson, mwilson@mail.arc.nasa.gov
University of California San Francisco, United States
Chenyu Wei, chenyu.wei@nasa.gov
University of California San Francisco, United States
Andrew Pohorille's group
Andrew Pohorille Michael Wilson Chenyu Wei Milan Mijajlovic

Cellular membranes with their hydrophobic interior are virtually impermeable to ions. Bulk of ion transport through them is enabled through ion channels. Ion channels of contemporary cells are complex protein molecules which span the membrane creating a cylindrical pore filled with water. Protocells, which are widely regarded as precursors to modern cells, had similarly impermeable membranes, but the set of proteins in their disposal was much simpler and more limited. We have been, therefore, exploring an idea that the first ion channels in protocellular membranes were formed by much smaller peptide molecules that could spontaneously self-assemble into short-lived cylindrical bundles in a membrane.

Earlier studies have shown that a group of peptides known as peptaibols is capable of forming ion channels in lipid bilayers when they are exposed to an electric field. Peptaibols are small, non-genetically encoded peptides produced by some fungi as a part of their system of defense against bacteria. They are usually only 14-20 residues long, which is just enough to span the membrane. Their sequence is characterized by the presence of non-standard amino acids which, interestingly, are also expected to have existed on the early earth. In particular, the presence of 2-aminoisobutyric acid (AIB) gives peptaibols strong helix forming propensities. Association of the helices inside membranes leads to the formation of cylindrical bundles, typically containing 4 to 10 monomers.

Although peptaibols are excellent candidates for models of the earliest ion channels their structures, which are stabilized only by van der Waals forces and occasional hydrogen bonds between neighboring helices, are not very stable. Although it might properly reflect protobiological reality, it is also a major obstacle in studying channel behavior. For this reason we focused on two members of the peptaibol family, trichotoxin and antiamoebin, which are characterized by a single conductance level. This indicates that their structures are unique and stable. In addition, it is also believed that the trichotoxin channel displays some selectivity between potassium and

chloride ions. This makes trichotoxin and antiamoebin ideal models of the earliest ion channels that could provide insight into the origins of ion conductance and selectivity.

In the absence of crystal structure of the trichotoxin and antiamoebin channels, we propose their molecular models based on experimentally determined number of monomers forming the bundles. We use molecular dynamics simulations to validate the models in terms of their conductance and selectivity. On the basis of our simulations we show that the emergence of channels built of small, α-helical peptides was protobiologically plausible and did not require highly specific amino acid sequences, which is a convenient evolutionary trait. Despite their simple structure, such channels could possess properties that, at the first sight, appear to require markedly larger complexity. To this end, we will discuss how the amino acid sequence and structure of primitive channels give rise to the phenomena of ionic conductance and selectivity across the earliest cell walls, which were essential functions for the emergence and early evolution of protocells. Furthermore, we will argue that even though architectures of membrane proteins are not nearly as diverse as those of water-soluble proteins, they are sufficiently flexible to adapt readily to the functional demands arising during evolution.